Dose Fractionation of Radiolabeled Antibodies in Patients with Metastatic Colon Cancer

Ruby F. Meredith, M.B. Khazaeli, Tiepu Liu, Gene Plott, Richard H. Wheeler, Charles Russell, David Colcher, Jeffrey Schlom, Dan Shochat, and Albert F. LoBuglio

Comprehensive Cancer Center, Departments of Radiation Oncology, Medicine, Nuclear Medicine, University of Alabama at Birmingham, and VA Medical Center, Birmingham, Alabama; University of Nebraska, Omaha, Nebraska; Lederle Laboratories, Pearl River, New York; and National Cancer Institute, Bethesda, Maryland

Twelve patients with metastatic colon cancer were treated with ^{131}I-chimeric B72.3 (IgG-4) at total doses of 28 or 36 mCi/m^2 in two or three weekly fractions. Bone marrow suppression was the only significant side effect. The degree of bone marrow suppression adjusted for whole-body dose was modestly but statistically significantly ($p = 0.04$) less than that seen with identical doses given as a single infusion for the total dose of 36 mCi/m^2. Nine of twelve patients developed an antibody response to ch B72.3, which altered the kinetics of radiolabeled antibody in four patients given a second course of therapy. One patient had a minor response that lasted 4 mo. Fractionation of this particular radiolabeled antibody at the dose schedule used produced a modest increase in the therapeutic window in regard to administered dose.

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Since their discovery in 1975, monoclonal antibodies have become the basis for promising new techniques for detecting and treating cancer (*1*). Despite the relative sparing of normal tissues by concentration of radioimmunoconjugates at tumor sites, bone marrow toxicity from the radiation has been a limiting factor. The most impressive response rate to radioimmunotherapy has been achieved with the escalation of radiation doses through the use of supportive autologous bone marrow transplantation (*2*). However, marrow transplantation is expensive, somewhat restricted by age and carries significant morbidity and mortality risks. Thus, methods to alleviate bone marrow suppression would be of considerable importance in advancing the use of radioimmunotherapy.

Classically, fractionation of radiation has been a means of increasing therapeutic gain by relatively sparing toxic effects in normal tissues compared to adjacent tumor sites (*3*). Although bone marrow stem cells are generally felt to be less influenced by fractionation than are other normal tissues, early clinical and animal studies of fractionated delivery of radioimmunotherapy suggest that larger doses of radiation are able to be administered with less marrow suppression than with single large doses (*4–7*). We have recently carried out a Phase I trial of ^{131}I-ch B72.3 administered as a single infusion (*8*). The maximally tolerated dose was 36 mCi/m^2 with marrow suppression as the dose limiting toxicity. In this second Phase I study, we have examined dose fractionation of ^{131}I-ch B72.3 in two and three weekly infusions.

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For reprints contact: Ruby F. Meredith, MD, PhD, University of Alabama at Birmingham, Department of Radiation Oncology, Wallace Tumor Institute-117, Birmingham, AL 35294-3300.

MATERIALS AND METHODS

Clinical Trial

The criteria for patient selection was identical to our prior Phase I trial (*8*). Ten male and two female patients (ages 43–71) with metastatic colorectal cancer, a Karnofsky performance status ≥60 and original tumor documented to be TAG-72 positive by immunoperoxidase technique (*9*) were entered into the clinical trial. Biopsy specimens of metastatic lesions from all patients were not available for TAG-72 determination. TAG-72 serum levels were quantitated pre-therapy using a commercial kit (CA72-4 radioimmunoassay, Centocor, Malvern, PA) as previously described (*10*). None of the patients had previous pelvic, chest or abdominal irradiation and all had been off chemotherapy for at least 4 wk. Prior to radioimmunotherapy, their WBC count was >3,500, platelet count >100,000, bilirubin <2.0 and estimated creatinine clearance was ≥50 cc/min. The treatment protocol had been reviewed and approved by the Institutional Review Board of the University of Alabama at Birmingham, and all patients gave informed consent.

Patients were treated at total radiation dose levels per course of 28 mCi/m^2 delivered in two 14 mCi/m^2 fractions on Days 1 and 8 (n = 3); 36 mCi/m^2 delivered in two 18 mCi/m^2 fractions on Days 1 and 8 (n = 6); or 36 mCi/m^2 delivered in three 12 mCi/m^2 fractions on Days 1, 8, and 15 (n = 3). Ten drops of saturated potassium iodide solution were prescribed beginning two days prior to administration of radioactive iodine and continuing daily for 14 days. Prior to each administration of radiolabeled antibody, a 100-μg test dose of unlabeled antibody was administered and the patient was carefully monitored for 30 min for evidence of an adverse reaction. If the test dose was well tolerated, 2-4.5 mg ^{131}I-ch B72.3 were infused over 1 hr. Vital signs were monitored every 15 min for 1 hr and then every 30 min six times. Subsequent to therapy, patients had serial gamma camera imaging, whole-body gamma counts and blood sampling

for pharmacokinetics and determination of an immune response against the administered antibody. Follow-up evaluation included history and physical exam, blood counts, liver, renal and thyroid function studies. Radiographic assessment of tumor response was done at 6 wk. Tumor response was defined as: complete response (CR) denoting disappearance of all evidence of tumor, partial response (PR) for ≥50% reduction of the product of the largest perpendicular diameters, minimal response (MR) for >25% but <50% regression, stable for <25% increase or decrease and progression for ≥25% increase in measured lesions and/or the appearance of new lesions.

Patients who responded or had stable disease were eligible for a repeat therapy ≥6 wk after the prior course at the same dose and schedule dependent upon recovery from hematologic toxicity and maintenance of performance status. Patients 2, 6, 9 and 12 received a second course and Patient 1 received five courses of therapy. Toxicity grading utilized the RTOG grading system (*11*) and a total bone marrow suppression score (grades of thrombocytopenia and leukopenia added together) was used for correlation analysis (*12*).

Dosimetry data collection by gamma camera imaging and whole-body gamma counts was as previously described (*13*). Data were collected after each infusion of a multi-fraction course. Assays for immune response against ch B72.3 were done using a double-antigen radiometric assay as previously described (*14*). A positive assay was defined as a post-therapy binding value at least two times the pre-therapy value and greater than 12 ng/ml. The upper limit of normal was established as 2 s.d. above the mean for 44 colon cancer patients who had not received monoclonal antibodies (5.4 ± 3.3 ng/ml).

Antibody

The chimeric B72.3 antibody was produced by Celltech, Ltd. and is composed of murine B72.3 V-region and constant regions of human IgG4 heavy chain and κ light chain (*15*). It was supplied in vials containing 7.69 mg (1.01 mg/ml) in 50 m*M* phosphate buffer by the National Cancer Institute, Division of Cancer Treatment under IND#3082. Radiolabeling at 10 mCi/mg antibody utilized a standard iodogen methodology (*16*). After determination of the percentage of iodine incorporation by instant thin-layer chromatography (*17*), free iodine was separated from ^{131}I-ch B72.3 by passage through a 1 × 22.5 cm acrylamide desalting column (Clinitics, Inc.). Quality control of the radiolabeled product included immunoreactivity by the method of Lindmo (*18*), HPLC analysis and Limulus amebocyte lysate assay. The level of free iodine after column chromatography was <1%. The amount of antibody infused varied from 2 to 4 mg.

Statistical Methods

Analyses of variance were used to test the difference of mean toxicity among fractions and treatment courses. Since the whole-body dose is related to toxicity, its effects were controlled by using analyses of covariance (*19*).

RESULTS

Side effects associated with the initial course of radiolabeled antibody were infrequent and mild. Five of 12 patients had transient low-grade fever (99.4-100.4°F) and one patient (#1) complained of transient nausea. On subsequent courses of therapy, Patient 12 had transient low-grade fever during his second course of therapy and Patient 1 had a transient mild drop in blood pressure during her fourth and fifth course of therapy. This blood pressure change lasted 15 min and did not require specific therapy.

The only other toxicity associated with this trial was the expected bone marrow suppression secondary to radiation exposure which produced nadir values of leukocytes and platelets at Day 35 to 50 of the study. Table 1 tabulates the nadir leukocyte and platelet counts for each patient and allows comparison with the dose/fractionation scheme and whole-body radiation dose. Figures 1 and 2 provide the mean toxicity scores and percent decrease from baseline for nadir leukocyte and platelet counts of patients in this trial as well as the patients from our previous Phase I trial who received an identical amount of ^{131}I-ch B72.3 in

TABLE 1
Comparison of Radiation Dose, Hematopoietic Toxicity, Tumor Localization and Response with Fractionated Therapy Using ^{131}I-ch B72.3

Patient no.	Dose (mCi/m²)	Schedule	Whole body (cGy)	WBC nadir (×1000)	Platelet nadir (×1000)	TAG-72 level (units/ml)	Radiolocalization	Response*
1	28	14 × 2	90	3.6	105	7	–	MR
2	28	14 × 2	102	3.6	113	5	–	P
3	28	14 × 2	79	6.4	136	66	+	P
4	36	18 × 2	135	3.1	43	112	–	P
5	36	18 × 2	105	3.1	69	19	–	P
6	36	18 × 2	99	3.2	152	19	–	S
7	36	18 × 2	111	1.9	95	61	–	P
8	36	18 × 2	109	4.2	127	220	–	P
9	36	18 × 2	139	4.1	136	2	–	S
10	36	12 × 3	106	4.0	196		+	P
11	36	12 × 3	121	2.7	96		+	P
12	36	12 × 3	99	4.3	125		+	S

* CR = complete response; PR = >50% tumor regression; MR = 25–50% tumor regression; S = <25% increase or decrease in tumor measurements; and P = >25% increase in tumor measurements and/or new lesions.

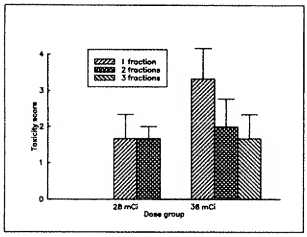


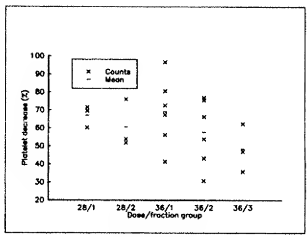
FIGURE 1. Comparison of mean toxicity score for groups of patients treated with total doses of 28 mCi/m^2 or 36 mCi/m^2 ^{131}I-ch B72.3 given as one, two or three fractions.

a single infusion (*8*). As seen in Figure 1, toxicity scores were modest and similar at 28 mCi/m^2 dose in single or double fractions. At 36 mCi/m^2, the mean toxicity scores were lower with two or three fractions compared to a single fraction, but the differences were not statistically significant.

In order to more carefully search for a biologic effect, we compared the difference of toxicity scores among the three groups at 36 mCi/m^2 using analysis of covariance to adjust for whole-body dose as well as baseline WBC and platelet counts. The adjusted means of toxicity score for one, two and three fraction groups were 3.28, 1.59 and 1.06, respectively. The difference in adjusted mean toxicity scores of one fraction compared with two fractions ($p = 0.043$) or three fractions ($p = 0.048$) were significant.

The mean nadir platelet and leukocyte counts from patients receiving single versus fractionated therapy were not significantly different. If analysis of covariance was used to control the whole-body dose, there was a significant difference between the adjusted mean platelet count for one (84.3×10^3/mm^3) and three fractions (149.5×10^3/mm^3) with a $p = 0.03$. The percent decrease of platelet or leukocyte counts at nadir compared to pre-therapy values (to control the effect of the whole body dose) is shown in Figures 2A-B. This analysis demonstrated a trend toward moderation of thrombocytopenia and leukopenia with fractionation, although the difference of the means was not significant.

Serial serum samples were used to estimate plasma half-life of the radiolabeled antibody by determining the percent injected dose of ^{131}I-ch B72.3 at each time point. With the initial course of therapy, the plasma half-life was 212 ± 22 hr, which was similar to that determined in our prior single fraction Phase I study (*10*). The repetitive infusions on day 8 or 15 had plasma disappearance curves which were similar to the day 1 curves.



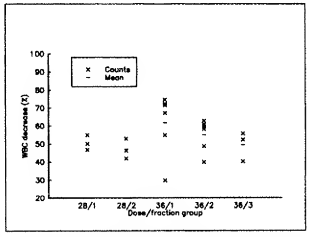


FIGURE 2. Comparison of toxicity for individual patients after 28 mCi/m^2 or 36 mCi/m^2 ^{131}I-ch B72.3 given as one, two or three fractions. Data are expressed as percent decrease of platelet (top) and white blood cell counts (bottom).

Table 2 presents the immune response of individual patients following initial infusion of ^{131}I-ch B72.3. Nine of 12 patients developed antibodies to ch B72.3 and the elevated levels were all competitively inhibited back to baseline values by an excess of unlabeled ch B72.3. For the data presented, the peak antibody responses tended to occur at 3–4 wk. However, four patients who had longer follow-up without re-treatment had peak antibody levels measured from 6.5 to 12 wk post-therapy.

The initial course of therapy resulted in 8/12 patients having disease progression, three patients with stable disease (#6, #9 and #12) and one patient (#1) with a minimal response, i.e., a 39% reduction in tumor size (Table 1). This 44-yr-old woman had multiple pulmonary metastasis as her only site of disease with cough and dyspnea on exertion. She had reduction of these symptoms following this initial course of therapy. She had received 28 mCi/m^2, whereas the three patients with stable disease received 36 mCi/m^2. There was no correlation between stable/MR

TABLE 2
Human Anti-ch B72.3 In Phase I Fractionation Trial

Patients	Pre-Rx	Day 15	Day 22	Day 28	Day 42
1	11*	72	116	68	33
2	5	41	51	31	19
3	5	5	—	85	—
4	6	5	—	5	7
5	6	8	18	92	101
6	7	16	52	22	29
7	8	9	18	15	12
8	12	20	—	301	281
9	9	10	11	13	26
10	13	14	14	15	14
11	11	11	10	12	11
12	13	14	44	76	44

* Results are expressed as ng of ^{125}I-ch B72.3 bound/ml sera.

status and tumor radiolocalization of isotope, dose administered or whole-body radiation dose estimates. It was impossible to estimate tumor radiation doses since positive images (Table 1) occurred on only one or two postinfusion days.

Five patients received a second course of therapy 8–10 wk following their initial treatment course (Table 3). This included the stable/MR patients as well as Patient 2 who had failed prior chemotherapy and was asymptomatic despite evidence of tumor progression. Two of these patients (#6 and #12) had large amounts of antibody to ch B72.3, which resulted in rapid clearance and excretion of the radiolabel as reflected in the dramatic reduction in whole-body radiation dose (Table 3). This ameliorated any evidence of marrow suppression and Patient 12 failed to have a positive localization in a previously radioimaged tumor site. Patients 1 and 2 had moderate antibody responses that had fallen toward normal at the time of second therapy. They had a moderate reduction in whole-body radiation doses. Patient 1 had a similar degree of marrow suppression, while Patient 2 had less marrow suppression and positive tumor imaging on Day 8. Patient 9 had a small antibody response which had returned to the normal range at the time of second infusion. This patient's whole-body dose was similar as on initial therapy and a greater degree of marrow suppression was noted after the second course of therapy. Patients 2, 6, 9 and 12 all had tumor progression at re-evaluation after the second course of therapy, which was approximately 4 mo after initial therapy. Patient 1 had a 45% reduction in tumor size at the time of second evaluation (Table 4) and went on to have a total of five courses of therapy (10 infusions) with a total dose of 140 mCi/m^2 over 10 mo. She persisted in having circulating antibody to ch B72.3 with low whole-body radiation doses reflecting the enhanced catabolism of the radiolabeled antibody (Table 4). At last follow-up (11/6/91), she was still active with moderate dyspnea on exertion 17 mo following initiation of this therapy and had received no other treatment modalities. Her pulmonary tumor burden was approximately twice her initial extent of disease.

DISCUSSION

Our initial Phase I trial of ^{131}I-ch B72.3 utilized a single infusion of radiolabeled antibody and resulted in a maximal tolerated dose of 36 mCi/m^2, which was lower than that for a number of xenogeneic ^{131}I-labeled antibodies (*2, 4, 20–22*). The relatively high degree of marrow suppression/mCi dose administered is related to the long effective half-life of this radiolabeled chimeric antibody, i.e., plasma half-lifeβ 224 ± 66 hr (*10*). Most normal tissues tolerate higher cumulative doses of external beam radiation when the dose is given as several smaller fractions separated by adequate repair time compared to a single tolerance dose (*3*). This strategy has led to fractionation schedules in animal models of radioimmunotherapy which demonstrate that larger doses of ^{131}I-labeled antibody can be administered and result in greater degrees of tumor regression as compared to single maximally tolerated doses (*5, 6, 23*). This trial examined the administration of ^{131}I-ch B72.3 administered in two or three fractions at weekly intervals and compared the toxicity/response to a prior single infusion study.

We chose a 1-wk interval between doses in order to complete treatment before the development of an immune

TABLE 3
Effect of Second Course of Fractionated Therapy with ^{131}I-ch B72.3

Patient no.	Dose schedule (mCi/m^2)	HACA* (ng/ml)	Whole-Body dose (cGy)		WBC nadir (×1000)		Platelet Nadir (×1000)		Radiolocalization		Response	
			1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	14 × 2	21	90	33	3.6	2.7	105	113	–	–	MR	MR
2	14 × 2	19	102	48	3.6	4.7	113	162	–	+	P	P
6	18 × 2	209	99	16	3.2	5.7	152	263	–	–	S	P
9	18 × 2	9	139	130	4.1	2.5	136	54	–	–	S	P
12	12 × 3	1180	99	17	4.3	4.8	125	168	+	–	S	P

* Levels at time of infusion of human anti-chimeric antibody (HACA).

TABLE 4
Effects of Repeated Courses of Therapy with ^{131}I-ch B72.3 in Patient 1

	Course of Therapy				
	#1	#2	#3	#4	#5
Dose (mCi/m^2)	14 × 2	14 × 2	14 × 2	14 × 2	14 × 2
Date	05/28/90 06/04/90	07/23/90 07/30/90	09/25/90 10/02/90	01/29/91 02/05/91	03/25/91 04/01/91
HACA (ng/ml)					
Peak value	—	116	34	21	29
Pre-treatment	11	21	14	9	29
Whole-body dose (cGy)	90	33	22	30	16
WBC nadir (×1000)	3.6	2.7	4.0	4.5	3.6
Platelet nadir (×1000)	105	113	110	100	97
Tumor measurements* (cm^2)	15.1	9.1	8.3	13.9	16.4
% reduction†	—	39	45	8	—

* Pre-therapy measurements are the sum of the product of bidimensional measurements of four index lesions.
† Percent reduction as compared to initial measurement of 15.1 cm^2.

response against the ch B72.3. More than half of the patients in our previous trial demonstrated elevated anti-ch B72.3 levels within 2 wk of initial exposure (*10*). Our choice of the relatively short interval between doses was also based on previous murine bone marrow studies suggesting repair of sublethal damage during low dose rate radiation and long-term tolerance of radiation at ≤3 cGy/hr (*24*, *25*), a dose rate which was estimated to be reached by 4 days after administration of ^{131}I-ch B72.3 for patients in this study. This fractionation schedule produced a biologically modest reduction in marrow suppression that would not likely allow a major increment in dose administered as compared to single infusion. This observation suggests that some repair occurred during the continuous radiation but that it was not sufficient to allow substantial increase in the dose of radioimmunoconjugate. A second factor may be that murine bone marrow is more tolerant of radiation of this type and may have more rapid marrow repair mechanisms (*26*).

The enhanced anti-tumor effects of fractionated schedules in animal models may not be solely due to increased dose administered. It is possible that a prior exposure to radiolabeled antibody could increase the sensitivity of tumor cells to a second exposure to radiolabeled antibody. In this regard, Marin et al. (*27*) have studied low dose rate radiation under in vitro conditions simulating those of radioimmunotherapy. They found that after 20 hr of low dose rate radiation glioblastoma cells were arrested in the radiosensitive G2/M phases of the cell cycle and the rate of cell kill increased. It is difficult to examine enhanced anti-tumor effects in our two Phase I trials. The first trial had no objective responses and four had stable disease outcomes in 12 patients, while this trial had one minimal response (45% decrease in tumor measurements) and three stable disease outcomes in 12 patients. However, it appears that Patient 1 did have a real reduction in tumor mass and alteration of the natural history of her disease secondary to therapy. She had many small (1-3 cm) lung metastases and we were not able to delineate tumor localization on Days 2 to 24. Thus, one would conclude that her tumors received a relatively low radiation dose rate (<1 cGy/hr) over a long duration with her first and possibly second cycle of therapy. Subsequent courses were limited by her immune response to ch B72.3. Our observation of tumor regression in Patient 1 supports several recent studies suggesting that exponentially decaying low dose radiation exposure may be able to produce anti-tumor effects at total doses below that predicted by traditional fractionated high dose rate radiation (*27*, *28*)

A second aspect of this trial was to examine the immune response to fractionated doses of ch B72.3. The incidence of immune response was 75% as compared to 58% in our prior trial of single dose therapy (*10*). No patient had antibodies present at the time of infusions on Day 8 or 15 and the plasma half-lives on these days were similar to Day 1 infusions. However, fractionation at greater intervals with this antibody could be problematic since many patients had antibody response ongoing at Day 22 or 28 (see Table 2). The effect of pre-existing antibody response to radiolabeled antibody is well illustrated in Table 3 with enhanced whole-body clearance of radioactivity. Only one of five patients was able to have a second cycle of therapy with comparable antibody kinetics as reflected in identical whole-body radiation dose estimates and plasma half-life. This patient had an increase in the degree of marrow suppression following the second course of therapy, suggesting a cumulative marrow radiation effect that was not seen in the other four patients with antibody enhanced radioactivity clearance (Table 3).

This study represents the first controlled trial of radiolabeled antibody fractionation in man. The schedule chosen produced minimal alteration of marrow tolerance to ^{131}I-ch B72.3. This probably reflects the long half-life of this antibody-isotope combination. There are several ways

in which future dose fractionated studies could be designed to improve on the results reported here. The first involves the isotype of the chimeric monoclonal antibody. We have previously shown (*29*) that ch B72.3 with the gamma 4 Fc has a much longer half-life than chimeric monoclonal antibodies with a gamma 1 Fc. The more rapidly clearing gamma 1 chimeric or antibody fragments would allow for less radiation damage to marrow. Along the same lines, longer time intervals between doses would provide more time for marrow repair. Another consideration in dose fractionation studies is the use of a monoclonal antibody whose variable region is non- or weakly immunogenic in humans. Previous studies (*8, 10, 30, 31*) have shown that the variable region of B72.3 is immunogenic in approximately half of patients to whom it is administered, either as a murine monoclonal antibody or in the chimeric (gamma 4) form. Preliminary studies (LoBuglio F, unpublished data) suggest that the second generation anti-TAG-72 monoclonal antibody, CC49, has a less immunogenic variable region and may thus be more suitable for dose fractionation studies. Radioimmunotherapy fractionation studies are deserving of continued investigation. Such studies require attention to human bone marrow repair time and duration of radiation exposure following injection of the radiolabeled reagent. Presumably, longer time intervals between antibody doses, or the use of an antibody molecule or fragment with shorter plasma half-life, would be more compatible with fractionation strategies in man.

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